REMARKS

Amendments to the Claims

Claims 8-9, 19, 25 and 26 have been canceled.

Claims 1, 7, 18, and 24 have been amended.

Claim 32 has been added.

Claim 1 has been amended to recite "autologous uncultured mesenchymal stem cells." Support for this amendment is found in the specification, for example, in originally-filed Claim 1 and at page 4, lines 22-25 and page 6, lines 8-11.

Claim 7 has been amended to recite "wherein an additional therapeutic agent is administered into the intervertebral disc, and wherein said additional therapeutic agent is a growth factor." Support for this amendment is found in the specification, for example, in originally-filed Claim 8 and at page 10, line 5 to page 11, line 2.

Claims 18 has been amended to recite the proper dependency.

Claim 24 has been amended to recite "wherein the needle bore has a maximum gauge of about 24 gauge." Support for this amendment is found in the specification, for example, in originally-filed Claim 24 and at page 12, lines 22-27.

Newly added Claim 32 recites "A method of treating degenerative disc disease in an intervertebral disc having a nucleus pulposus, comprising administering a growth factor in the TGF-β superfamily and autologous uncultured mesenchymal stem cells embedded in collagen gel into a degenerated intervertebral disc." Support for this amendment is found in the specification, for example, at page 10, lines 5-24.

No new matter has been added. Therefore, entry of the amendments into the application is respectfully requested.

Amendment to the Specification

The specification has been amended to update the status of related applications.

No new matter has been added. Therefore, entry of the amendments into the application is respectfully requested.

Information Disclosure Statement

Applicants note that reference AT13, which was cited in Applicants' Information Disclosure Statement, is not material to patentability. The reference was downloaded on December 9, 2005 and merely discusses viscosupplementation.

Priority

The pending claims are entitled to at least claim the benefit of priority application USSN 10/456,948, filed June 6, 2003. Applicants direct the Examiner's attention to the fact that USSN 10/456,948 provides support for administering autologous mesenchymal stem cells. (See the specification of USSN 10/456,948, for example, at page 21, line 28 to page 22, line 9).

Rejection of Claims 1-26 and 31 under 35 U.S.C. § 112, first paragraph

The Examiner has rejected Claims 1-26 and 31 under 35 U.S.C. § 112, first paragraph, as lacking enablement. The Examiner states that, although the specification is enabling for a method of treating an animal model of degenerative disc disease by administering mesenchymal stem cells embedded in Atocollagen gel with additional TGF-β, it does not reasonably provide enablement for treating degenerative disc disease comprising administering "generic" autologous cells" using a "generic carrier" wherein "an additional therapeutic agent" is added.

Claims 8, 9, 19 and 25-26 have been canceled.

In regard to autologous cells, the Examiner states that these cells could be thousands of cell types, and, while the art teaches that use of autologous mesenchymal cells from bone marrow can be appropriate for treatment of degenerative disc disease, it is silent with regard to the use of generic autologous cells. While Applicants respectfully disagree with the Examiner, in order to further prosecution, Applicants have amended Claim 1 to recite "autologous uncultured mesenchymal stem cells." Claims 2-7, 10-18, 20-24 and 31 depend upon Claim 1, and, therefore, contain the same limitation.

In regard to additional therapeutic agents, the Examiner states that while the art teaches that TGF-β is useful for modulating the chondrocytic phenotype in mesenchymal stem cells, it is silent as to the usefulness of other therapeutic agents. While Applicants respectfully disagree with the Examiner, in order to further prosecution, Applicants have amended Claim 7 to recite

that the additional therapeutic agent is a growth factor. TGF-β is a growth factor, and one of skill in the art at the time the invention was made would be able to administer other growth factors and to determine their efficacy in the claimed invention. Applicants have also amended Claim 18 to recite the method of Claim 7, wherein the additional therapeutic agent is TGF-β.

In regard to carriers, the Examiner states that post-filing date art also suggest that the carrier hyaluronan is not appropriate for use as a hydrogel for long-term retention of mesenchymal cells at the locus of action of the degenerative disc disease. According to the Examiner, although it possesses several desirable properties, it does not result in long-term retention of such cells, and, thus, predictability of the appropriate carrier is low.

Applicants note that the carrier hyaluronan is known to be routinely used safely and effectively in humans. In addition, contrary to the Examiner's position, it is not necessary, and, in fact, it may be undesirable, to use carriers that retain cells long term when treating degenerative disc disease. This is because there is limited space in the degenerative disc space and because the mesenchymal stem cells, once delivered to the degenerative disc space, begin to act on their own without the need for a carrier. Once the stem cells start to become nucleus pulposus and start to form the matrix, carriers are no longer needed. Therefore, a carrier that does not cause long term retention of mesenchymal stem cells is useful in the claimed invention.

The claims, particularly as amended, are enabled. Reconsideration and withdrawal of the rejection are respectfully requested.

Rejection of Claims 1-26 and 31 under 35 U.S.C. § 112, first paragraph

The Examiner has rejected Claims 1-26 and 31 under 35 U.S.C. § 112, first paragraph, on the grounds that they lack written description. The Examiner states that the claims lack written description for "uncultured cells" and "carriers."

A patent specification satisfies the written description requirement when it describes the claimed invention in sufficient detail that one skilled in the art can reasonable conclude that the inventor had possession of the claimed invention. MPEP § 2163 (revision August 2006). The Applicant must convey with "reasonable clarity" to those skilled in the art that he or she was in possession of the claimed invention as of the filing date.

In regard to the rejection of "uncultured cells," the Examiner states that the claims encompass unknown and undisclosed cells. While Applicants respectfully disagree, in order to further prosecution, Applicants have amended Claim 1 to recite "autologous uncultured mesenchymal stem cells." This element was well-known in the art, and is literally supported and described in the specification. See, for example, specification, page 4, lines 22-25: "The present inventors have developed an intra-operative procedure for efficaciously treating degenerative disc disease by introducing autologous uncultured cells, (e.g., mesenchymal stem cells or chondrocytes or fibroblasts) into the patient's disc". See also page 6, lines 8-11, of the specification. Claims 2-7, 10-18, 20-24 and 31 depend upon Claim 1, and, therefore, contain the same limitation. Claims 8-9, 19 and 25-26 have been canceled.

In regard to the rejection of "carriers," Applicants are not claiming a "generic" carrier, but rather specific carriers, such as beads, microspheres, nanospheres, hydrogels, gels, polymers, ceramics, collagen and platelet gels. These carriers are described in the specification. See the specification, for example, at page 7, line 9 to page 9, line 3. All of these terms were well-known in the art and described in the specification with "reasonable clarity" such that one of ordinary skill in the art would understand that Applicants were in possession of the claimed carriers.

Reconsideration and withdrawal of the rejection are respectfully requested.

Rejection of Claim 24 under 35 U.S.C. 112, second paragraph

Claim 24 has been rejected under 35 U.S.C. § 112, second paragraph as being indefinite in the recitation of "maximum gauge of about 24 gauge."

Applicants have amended Claim 24 to recite "wherein the needle bore has a maximum gauge of about 24 gauge." One of ordinary skill in the art would understand that a maximum gauge of a needle bore refers to diameter. Thus, as the Examiner properly noted, 30 gauge would fall within the scope of the claim.

Reconsideration and withdrawal of the rejection are respectfully requested.

Rejection of Claims 1-3, 5-16, 20-26 and 31 under 35 U.S.C. § 103(a)

The Examiner has rejected Claims 1-3, 5-16, 20-26 and 31 under 35 U.S.C. § 103 as being unpatentable over Sakai *et al.*, "Transplantation of Mesenchymal Stem Cells Embedded in Atelocollagen® Gel to the Intervertebral Disc: A Potential Therapeutic Model for Disc Degeneration," *Biomaterials, 24*: 3531-3541 (September 2003) ("Sakai"). The Examiner states that "Sakai does not teach injecting the autologous mesenchymal stem cells without culture. However, it would be obvious to do so, since the role of culturing is simply to add a marker to the cells so that the cells can be distinguished from cells that have not been isolated."

Applicants respectfully disagree. Sakai was published in September 2003. As discussed above, Applicants are entitled to a priority date of USSN 10/456,948, filed June 6, 2003. Thus, Sakai is not eligible as prior art because it was published after this priority date.

However, even if Sakai were prior art, Sakai does not teach or suggest Applicants' claimed invention, and would not motivate. Applicants are the first to disclose treatment of degenerative disc disease in an intervertebral disc having a nucleus pulposus, comprising administering autologous uncultured mesenchymal stem cells into a degenerated intervertebral disc. Sakai discloses use of cultured mesenchymal stem cells for the treatment of intervertebral disc degeneration, using a rabbit model. One of ordinary skill in the art would not be motivated to practice Applicants' claimed invention with a reasonable expectation of success based on the teachings of Sakai.

The Examiner suggests that, although Sakai teaches injecting cultured stem cells, "the role of culturing is simply to add a marker to the cells so that the cells can be distinguished from cells that have not been isolated". Applicants respectfully note that this is incorrect. The mesenchymal stem cells of Sakai were first cultured for 12-15 days. (See section 2.1 of Sakai). Only then were the cultured cells infected overnight with the adenovirus containing the marker. (See section 2.2 of Sakai). According to the Examiner, there would be a reasonable expectation of success because cells that were in culture for weeks, such as in Sakai *et al.*, are still "viable and therapeutic". Applicants respectfully disagree.

First, Sakai's method would result in magnifying contamination of the cell population. For example, culturing stem cells may result in magnifying contamination from other cells, such

as fibroblast cells, which grow ten times faster than stem cells. Thus, culturing stem cells does not result in a pure stem cell population.

Second, Sakai's method cannot be used as a therapeutic. Culturing stem cells involves expanding the cell population by adding solutions, such as Dulbecco's modified eagle media (DMEM). DMEM contains phenol which is a hazardous chemical to the human body.

Third, Sakai's culturing of stem cells would not be desirable for treatment of degenerative disc disease because culturing results in a large stem cell population. When treating degenerative disc disease, it is not desirable to have a large stem cell population because one would not want to overburden the bodily system with nutritional requirements for feeding large numbers of such cells. In addition, the degenerative disc can only hold a limited number of cells.

Moreover, Applicants' claimed method of administering uncultured mesenchymal stem cells is advantageous because the process permits the patient to undergo the procedure of removal of cells from the bone marrow while the patient is already under general anesthesia to undergo the surgery required to administer the cells to the degenerative disc. In contrast, when the stem cells are cultured, two costly procedures are required – first, the patient must undergo general anesthesia to undergo the painful procedure of removal of the cells from the bone marrow and then the patient must undergo general anesthesia again to undergo the surgery required to administer the cells to the degenerative disc.

Thus, as noted above, since Sakai was published after Applicants' priority date, it is not eligible as prior art. However, even it were, Sakai would not render obvious Applicant's claimed invention, because there would not be a reasonable expectation of success that Sakai's methods would be useful as a therapeutic.

Reconsideration and withdrawal of the rejection are respectfully requested.

CONCLUSION

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned.

Respectfully submitted,

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